IN THE U.S. PATENT AND TRADEMARK OFFICE

Applicants: Brazzell et al. Conf. No.: 9942

Application No.: 10/080,797 Art Unit: 1635

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Title: METHOD FOR TREATING OCULAR NEOVASCULARIZATION

SECOND DECLARATION OF SHEILA CONNELLY

I, Sheila Connelly, do hereby declare and state:

1) My qualifications are as presented in the First Declaration of Connelly dated 6 February 2006 (hereinafter "my First Declaration"). I am familiar with gene therapy, anti-angiogenesis pathology in the eye.

2) I read and understand Leboulch et al. (WO 99/26480), and for the following reasons, conclude that the Leboulch et al. non-patent reference does not provide one with sufficient direction to use endostatin to treat anti-angiogenesis associated with non-cancer conditions in the eye.

3) As mentioned in my First Declaration, at the time Leboulch et al. was published, it was known that the early in vitro results with endostatin could not be repeated by many investigators. The problems with endostatin first became widely recognized through an article in the Wall Street Journal on November 12, 1998 entitled Novel Cancer Approach Stumbles as Others Fail to Repeat Successes. The article then noted that Dr. Bjorn Olsen a consultant of EntreMed (the company commercializing endostatin), who had originally worked with the Folkman lab in isolating endostatin, was unable to reproduce Dr. Folkman's results. Finally, near the end of the article, Dr. Olsen noted that "...one possibility is that some unknown contaminant was causing the tumor-shrinking power in mice."

4) The prevailing attitude at the time of Leboulch et al. was significant skepticism about the therapeutic utility of endostatin.

5) Leboulch et al. provide a superficial treatment on the alleged use of endostatin to inhibit solid tumor growth, see the Summary of the Invention of Leboulch et al.

6) On page 5, Leboulch et al. alleges that any of a variety of vectors can be used for the delivery of endostatin. Although each vector has unique characteristics, details on the making and using of a vector to deliver endostatin are provided only for a single type of vector in Leboulch et al., a murine retrovirus.

7) Beginning at page 6, Leboulch et al. teach using fragments and fusion proteins. In light of the prevailing opinion on the impossibility of having full length endostatin operate to treat cancer, it is impossible to know whether a fragment would operate to treat cancer.

8) Beginning at page 11, Leboulch et al. teach administration for the treatment of solid tumors. Every possible means are disclosed. However, it is known that obtaining effective concentrations of drugs at the required site in the body is difficult, and certainly with respect to solid tumors which can be in remote and inaccessible sites in the body.

9) As noted in the paragraph spanning pages 13 and 14, Leboulch et al. recognize the unpredictability of having endostatin function for treating cancer, and then provide a generic listing of tissues without any discussion of a particular vector or target cell type, etc. For example, it is known that retroviral vectors do not infect all cell types. While the eye is mentioned, there is no teaching how to deliver a vector and what cells to infect, for example.

10) I was advised that many of the Examples were not actually conducted. That adds to greater uncertainty and leads me to the conclusion that WO 99/26480 does not provide me with any information that endostatin is antiangiogenic in the eye. Apparently, the only experiments actually conducted are: Examples 2 and 3, where various murine retroviral vectors carrying different forms of inserts, but not full length endostatin alone, were constructed, and of those, only five constructs contain endostatin and those were fusion proteins with angiostatin; Example 4, where no vectors containing endostatin were tested; and Example 5, where a fusion protein was used, but it is not known which fusion protein of Example 2 was tested, and the vector was transduced directly into cancer cells. I was told that all of the remaining examples were not actually conducted.

11) Thus, only one vector system was taught, there was no demonstration on the successful expression of endostatin, there were no experiments on the use of endostatin in the eye, and there was no demonstration on the use of endostatin for treating non-cancer diseases.

CONCLUSION

12) Thus, when I reviewed Leboulch et al., I concluded there was insufficient information for me to know how to use endostatin as an antiangiogenic molecule for treating a non-cancer condition of the eye. That conclusion was compounded by the prevailing knowledge that endostatin research could not be reproduced. There is no evidence in Leboulch et al. that endostatin could be expressed in the eye. There is no evidence in Leboulch et al. that endostatin could be used to treat non-cancer disorders. There is no evidence in Leboulch et al. that endostatin can or could be used to treat an ocular non-cancer disorder.

13) Thus, the methods of WO 99/26480 are not reproducible. There is no way to conclude that WO 99/26480 would allow me to use endostatin to treat an ocular non-cancer disorder.

All statements made herein of my own knowledge are true and that all statements made on information and belief are true; and further that the statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the patent application in the United States of America or any patent issuing therefrom.

April 28, 2006
Date

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